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Total Synthesis of Incarviditone and Incarvilleatone**

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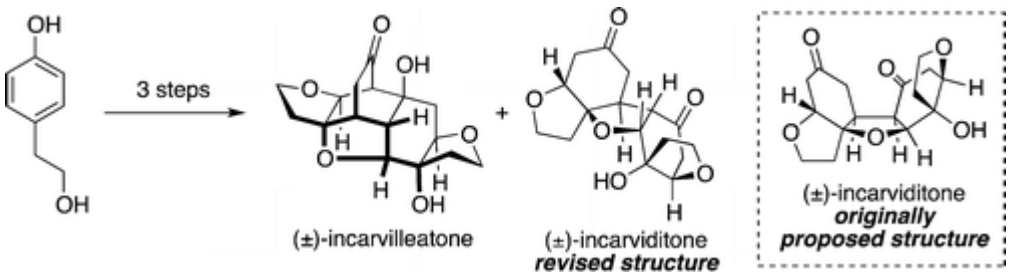
Supporting information:
Experimental procedures and analytical data for all compounds, and atomic displacement ellipsoid plots for compound 9 (CCDC 897209). This material is available free of charge via the Internet at http://pubs.acs.org

Graphical abstract:

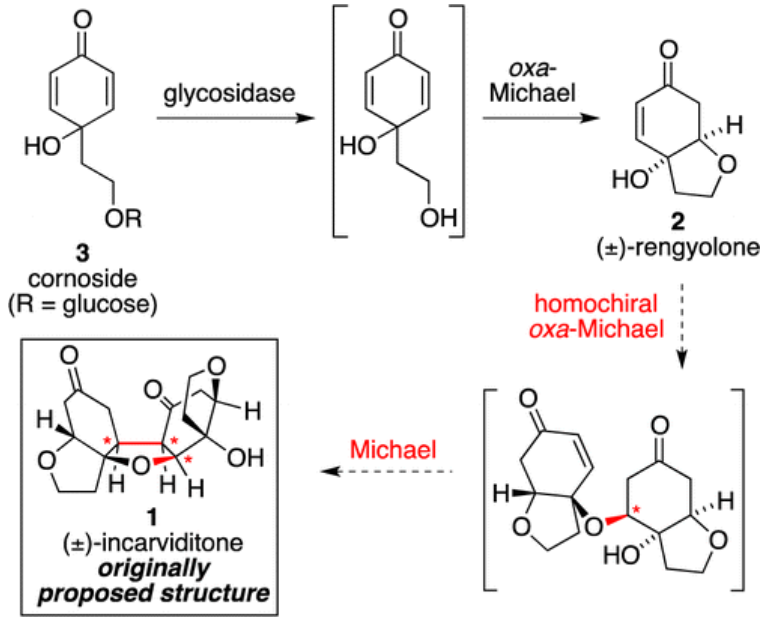


Abstract

The total synthesis of the racemic natural products (±)-incarviditone and (±)-incarvilleatone has been accomplished in three steps *via* biomimetic dimerization of (±)-rengyolone. Homochiral dimerization of (±)-rengyolone affords (±)-incarviditone through a domino *oxa*-Michael/Michael sequence. Heterochiral dimerization, involving a domino *oxa*-Michael/Michael/aldol reaction sequence, affords (±)-incarvilleatone. Single crystal X-ray analysis of a derivative of (±)-incarviditone has resulted in revision of the originally proposed structure.

Main text

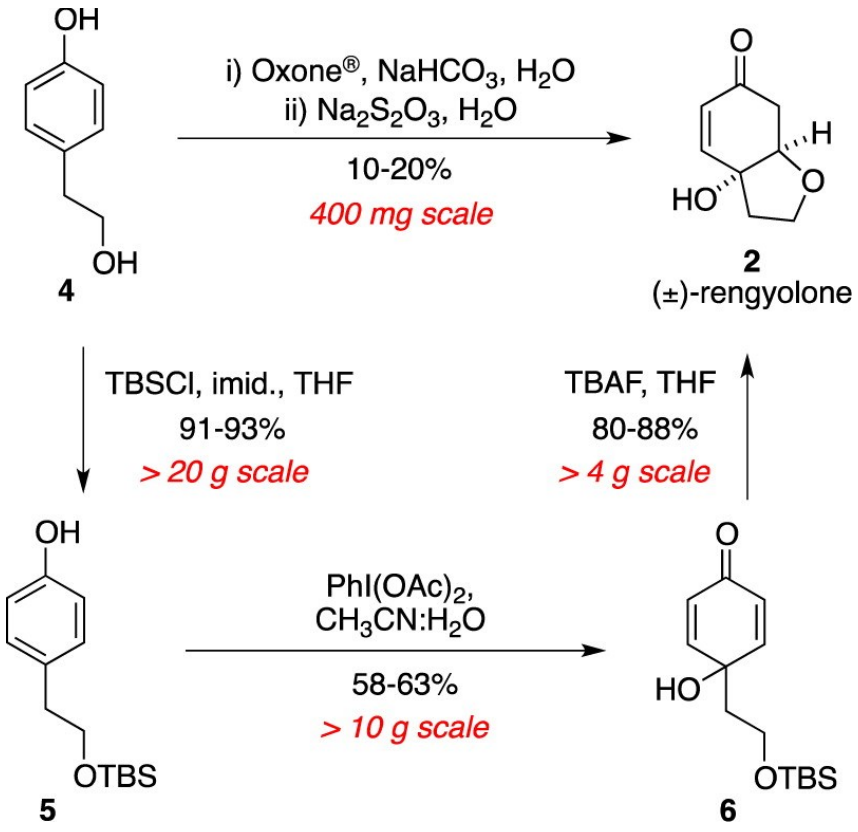
The racemic natural product (±)-incarviditone (**1**) was isolated in 2009 by Zhang and co-workers from *Incarvillea delevayi*.[1] In the isolation paper, Zhang noted that (±)-incarviditone (**1**) was a dimer of the co-isolated natural product (±)-rengyolone (**2**; synonyms: halleridone, cleroindicin F),[2] although no mechanism for this dimerization was presented. A plausible biosynthesis of (±)-incarviditone (**1**) from the *para*-quinolethanoid glycoside natural products, *e.g.* cornoside (**3**),[3] is depicted in Scheme 1. Thus, upon cleavage of the glycosidic bond, the putative aglycone undergoes an intramolecular *oxa*-Michael reaction to afford (±)-rengyolone (**2**).[4] Dimerization of (±)-rengyolone (**2**) then occurs through a domino *oxa*-Michael/Michael sequence to form (±)-incarviditone (**1**). This hypothesis involves two 'like' enantiomers reacting together (*i.e.* a homochiral dimerization) to afford a single diastereomeric product as a racemate (Scheme 1). The origin and magnitude of this apparent stereoselectivity, which presumably is non-enzymatic, was immediately intriguing to us. Therefore, we embarked upon a biomimetic synthesis of (±)-incarviditone (**1**).



Scheme 1. Proposed biogenesis of (±)-incarviditone (**1**).

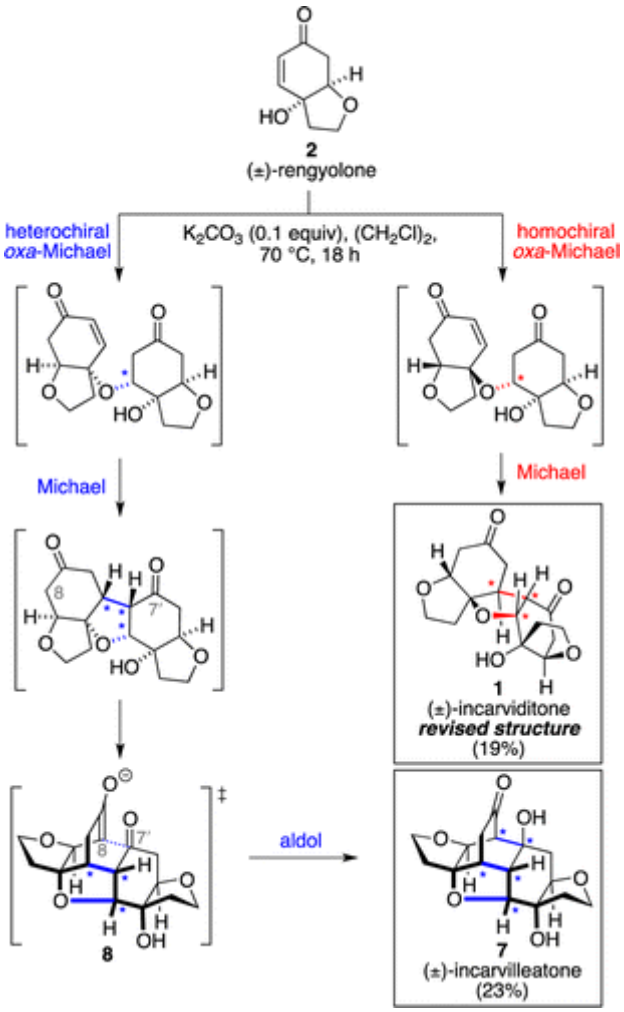
As noted by Nising and Bräse,[5] the reversible nature of *oxa*-Michael reactions has precluded their general application in synthesis. Nevertheless, we were encouraged by the likelihood that our *oxa*-Michael adduct would be trapped through an essentially irreversible *carbo*-Michael reaction.[5]

Confident in our proposed domino Michael strategy we first required access to (±)-rengyolone (**2**). The synthesis of (±)-rengyolone (**2**) from commercially available phenol **4** has been reported by several groups.[6] Photosensitized generation and addition of singlet oxygen has been explored in detail with only moderate yields of (±)-rengyolone (**2**) obtained.[6a,b] Carreño and Urbano have described the same transformation using Oxone®/$NaHCO_3$ in water and, following a same-pot $Na_2S_2O_3$ reduction, obtained a 50% yield of (±)-rengyolone (**2**).[6c] In our hands this protocol invariably gave low yields (10-20%) and was difficult to scale-up (Scheme 2);[7] work is ongoing in our laboratory to optimize this one-pot procedure. With a need for larger quantities of (±)-rengyolone (**2**), we elected to devise a new practical, reliable and scalable synthetic route (Scheme 2). The PIDA oxidation of phenol **5** is a known transformation[6d] and the resultant *para*-quinol **6** can be viewed as a synthetic equivalent of cornoside (**3**). Pleasingly, when treated with TBAF, *para*-quinol **6** afforded (±)-rengyolone (**2**) in high yield.[8] This three step sequence was easily scaled up to afford multi-gram quantities of (±)-rengyolone (**2**).



Scheme 2. Synthesis of (±)-rengyolone (**2**).[6c,d, 7]

Our initial efforts at the biomimetic dimerization of (±)-rengyolone (**2**) using acid catalysis and iminium ion catalysis were unsuccessful. The likely explanation is the poor nucleophilicity of the tertiary alcohol. Following a screen of basic reaction conditions, including Taylor's stoichiometric LiOH/THF[10] and Carreño's stoichiometric NaH/CH_2Cl_2 conditions,[11] we were delighted to find that catalytic K_2CO_3 in $(CH_2Cl)_2$ was sufficient for the dimerization of (±)-rengyolone (**2**). Thus, one gram of (±)-rengyolone (**2**) was treated to 10 mol % K_2CO_3 in 0.4 mL of $(CH_2Cl)_2$ at 70 °C for 18 h. Following flash chromatography, (±)-incarviditone (**1**) was isolated in 19% yield and the remaining (±)-rengyolone (**2**) was recovered in 6% yield (Scheme 3).

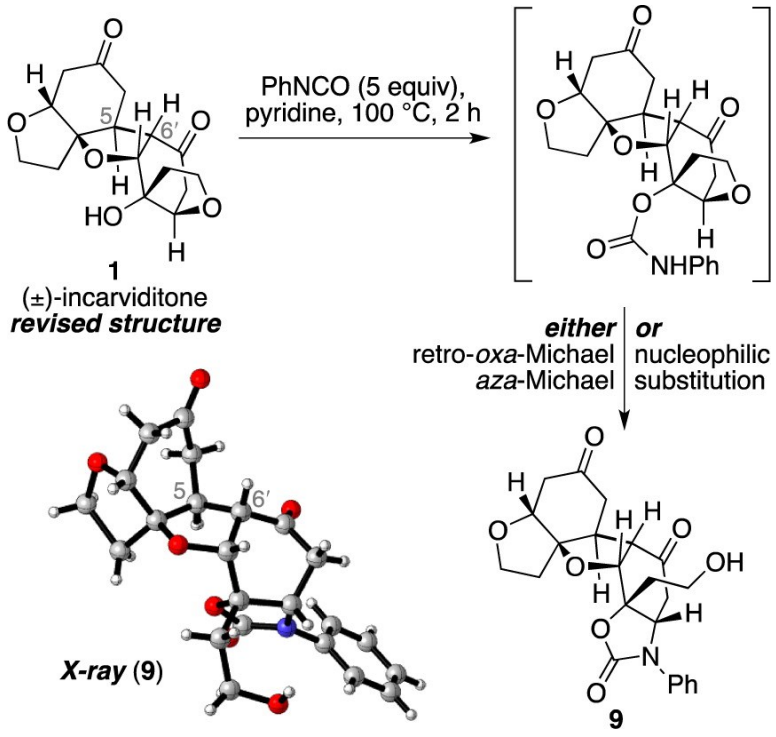


Scheme 3. Biomimetic synthesis of (±)-incarviditone (**1**) and (±)-incarvilleatone (**7**), with the proposed intermediates.

The spectroscopic data for our synthetic (±)-incarviditone (**1**) matched perfectly with that reported by Zhang and co-workers,[1,8] thus confirming that the total synthesis had been achieved. The structure reported for the natural product by Zhang and co-workers was based on their analysis of NMR data. Upon re-evaluation of this

data we concluded that, although the connectivity of (±)-incarviditone (**1**) was secure, the relative stereochemistry could not be unequivocally established. After numerous attempts to grow crystals of (±)-incarviditone (**1**) and its derivatives, we finally discovered that treatment of (±)-incarviditone (**1**) to excess phenyl isocyanate in pyridine at 100 °C afforded crystalline oxazolidinone **9** (Scheme 4).[9] Single crystal X-ray analysis of **9**, which is presumably formed through a sequence involving carbamate formation, retro-*oxa*-Michael addition and *aza*-Michael addition, revealed a *trans*-configuration between C5 and C6′ at the central tetrahydrofuran ring. The structure originally assigned to (±)-incarviditone (**1**) (Scheme 1), with a *cis*-configuration between these two stereocentres is incorrect and must be revised to that shown in Schemes 3 and 4.

Compound **7**, a further isomeric dimer of (±)-rengyolone (**2**), was also isolated in 23% yield (Scheme 3). During the preparation of this manuscript, Zhang and co-workers disclosed the isolation of (±)-incarvilleatone (**7**) from *Incarvillea younghusbandii*.[12] The physical and spectroscopic data reported for this natural product matched perfectly with that of our synthetic dimer (Scheme 3).[8] The structure of (±)-incarvilleatone (**7**) was secured by Zhang and co-workers using single crystal X-ray analysis.[12] Therefore, we report the first total syntheses of both these complex polycyclic natural products. The biosynthesis of (±)-incarvilleatone (**7**) involves the union of two 'unlike' enantiomers of rengyolone (**2**) (*i.e.* a heterochiral dimerization). We propose a domino *oxa*-Michael/Michael/aldol biosynthetic reaction sequence from rengyolone (**2**) to (±)-incarvilleatone (**7**) (Scheme 3).[13] The difference in product outcome for the homochiral and heterochiral dimerization pathways appears to stem from the ability of the latter to adopt transition state **8** (Scheme 3).



Scheme 4. Formation and crystal structure of compound **9**.

In summary, the synthetic work outlined in this communication provides strong evidence that (±)-rengyolone (**2**) undergoes domino sequences of nucleophilic addition reactions in nature to afford *both* (±)-incarviditone (**1**) and (±)-incarvilleatone (**7**).[14] It is well established that imitating nature in synthesis has many anticipated benefits[15] but this work also highlights an unexpected one. Our synthesis of (±)-incarvilleatone (**7**) is the more impressive of the two, with 7 new bonds, 4 new rings and 9 new stereocentres formed in just three steps, and yet was neither planned nor even considered at the outset.[16] This serendipitous result is a direct result of following a biomimetic approach.

Notes and references

[1] Chen, Y. Q. ; Shen, Y. H.; Su, Y. Q.; Kong, L. Y.; Zhang, W. D. *Chem. Biodiversity* **2009**, *6,* 779-783.

[2] (a) Endo, K.; Hikino, H. *Can. J. Chem.* **1984**, *62,* 2011-2014. (b) Messana, I.; Sperandei, M.; Multari, G.; Galeffi, C.; Marini Bettolo, G. B. *Phytochemistry* **1984**, *23,* 2617-2619. (c) Tian, J.; Zhao, Q. S.; Zhang, H. J.; Lin, Z. W.; Sun, H. D. *J. Nat. Prod.* **1997**, *60,* 766-769.

[3] Isolation of cornoside: (a) Rosendal, J. S.; Kjaer, A.; Juhl, N. B. *Acta. Chem. Scand.* **1973**, *27,* 367-369. For a review of C_6C_2 glycosides see: (b) Jimenez, C.; Riguera, R. *Nat. Prod. Rep.* **1994**, *11,* 591-606.

[4] It has been shown that enzymatic hydrolysis of cornoside affords rengyolone directly.[6b]

[5] (a) Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2008**, *37,* 1218-1228. (b) Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2012**, *41,* 988-999.

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[7] The yields we have obtained for the Oxone®/$NaHCO_3$ reaction are in agreement with the yield reported by Prof. You.[6e]

[8] The NMR spectra of (±)-rengyolone (**2**), (±)-incarviditone (**1**) and (±)-incarvilleatone (**7**) all show concentration dependency in chemical shifts, see the Supporting Information for details.

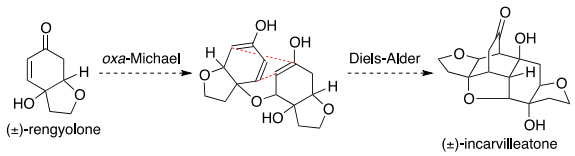
[9] Agarwal, K. L.; Khorana, H. G. *J. Am. Chem. Soc.* **1972**, *94,* 3578-3585.

[10] Greatrex, B. W.; Kimber, M. C.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2003**, *68,* 4239-4246.

[11] Cerrano, M. C.; Ribagorda, M. *Org. Lett.* **2003**, *5,* 2425-2428.

[12] Gao, Y. P.; Shen, Y. H.; Zhang, S. D.; Tian, J. M.; Zeng, H. W.; Ye, J.; Li, H. L.; Shan, L.; Zhang, W. D. *Org. Lett.* **2012**, *14,* 1954-1957.

[13] Prof. Zhang proposed a different biosynthetic hypothesis for (±)-incarvilleatone, involving an *oxa*-Michael/intramolecular-Diels-Alder sequence:[12]



[14] The possibility that (±)-incarviditone (**1**) and (±)-incarvilleatone (**7**) are formed during the isolation process can not be ruled out. However, during our attempts to mimic the isolation conditions (rengyolone (**2**) in EtOH, 78 °C, 24 h) no trace of either dimer was observed *via* ^{1}H NMR.

[15] For a recent perspective on biomimetic syntheses see: Razzak, M.; De Brabander, J. K. *Nat. Chem. Biol.* **2011**, *7,* 865-875.

[16] For a recent example of a biomimetic approach yielding a natural product prior to isolation from natural sources see: Lawrence, A. L.; Adlington, R. M.; Baldwin, J. E.; Lee, V.; Kershaw, J. A.; Thompson, A. L. *Org. Lett.* **2010**, *12,* 1676-1679.